Nexavar® (sorafenib) tablets

Dear Healthcare Professional,

NEXAVAR® (sorafenib) is NOW APPROVED for the treatment of patients with locally recurrent or metastatic, progressive, differentiated thyroid carcinoma (DTC) that is refractory to radioactive iodine treatment.[1]

Important Safety Considerations

- NEXAVAR in combination with carboplatin and paclitaxel is contraindicated in patients with squamous cell lung cancer
- Cardiac ischemia and/or myocardial infarction may occur. The incidence of cardiac ischemia/infarction in NEXAVAR-treated vs placebo-treated patients was 1.9% vs 0% in the DTC study. Temporary or permanent discontinuation of NEXAVAR should be considered in patients who develop cardiac ischemia and/or myocardial infarction

NEXAVAR was studied in DECISION,* a phase 3, international, multicenter, randomized, double-blind, placebo-controlled trial including 417 patients with locally recurrent or metastatic, progressive, differentiated thyroid carcinoma refractory to radioactive iodine (RAI) treatment.[1]

Progression-free survival (PFS) was the major efficacy outcome measure used in the study. Additional efficacy outcome measures included overall survival, tumor response rate, and duration of response. PFS was evaluated by blinded independent radiological review using modified RECIST† criteria.[1‡]

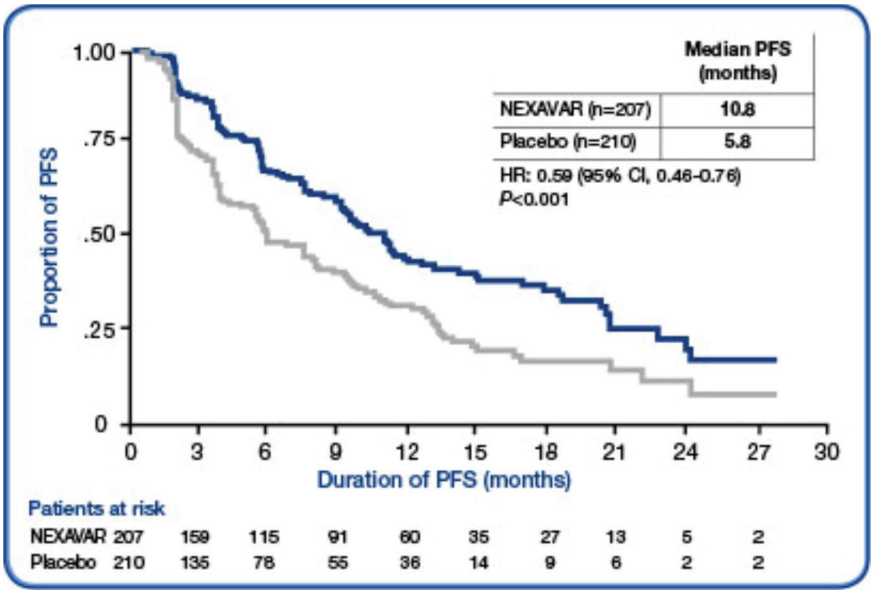
Patients were included in the study if they experienced progression within 14 months of enrollment and had DTC refractory to radioactive iodine treatment. RAI-refractory disease was defined based on 4 criteria that were not mutually exclusive[1]:

- A target lesion with no iodine uptake on an RAI scan (68% of patients)
- Tumors with iodine uptake and progression after RAI treatment within 16 months of enrollment (12% of patients)
- Tumors with iodine uptake and multiple RAI treatments with the last treatment greater than 16 months prior to enrollment, and disease progression after each of 2 RAI treatments administered within 16 months of each other (7% of patients)
- Cumulative RAI dose ≥ 600 mCi administered (34% of patients)

Note: All RAI treatments and diagnostic scans were to be performed under conditions of a low-iodine diet and adequate TSH stimulation.

The DECISION Study demonstrated median PFS of 10.8 months with NEXAVAR (95% confidence interval [CI], 9.1-12.9) versus 5.8 months with placebo (95% CI, 5.3-7.8). The hazard ratio (HR) was 0.59; 95% CI, 0.46-0.76; $P < 0.001$.[1]

Kaplan-Meier Curve of PFS in DTC Study[1]



The most common adverse reactions reported for NEXAVAR-treated patients vs placebo-treated patients in DTC, respectively, were: Palmar-plantar erythrodysesthesia syndrome (PPES) (69% vs 8%), diarrhea (68% vs 15%), alopecia (67% vs 8%), weight loss (49% vs 14%), fatigue (41% vs 20%), hypertension (41% vs 12%), rash (35% vs 7%), decreased appetite (30% vs 5%), stomatitis (24% vs 3%), nausea (21% vs 12%), pruritus (20% vs 11%), and abdominal pain (20% vs 7%). Grade 3/4 adverse reactions were 65% vs 30%.[1]

Important Safety Considerations (continued)

- An increased risk of bleeding may occur following NEXAVAR administration. In the DTC study, the following bleeding adverse reactions were reported in the NEXAVAR-treated vs placebo-treated patients, respectively, bleeding (17.4% vs 9.6%) and Grade 3 bleeding (1% vs 1.4%). If bleeding necessitates medical intervention, consider permanent discontinuation of NEXAVAR
- Hypertension may occur early in the course of treatment. Monitor blood pressure weekly during the first 6 weeks and periodically thereafter, and treat, if required
- Hand-foot skin reaction and rash are common and management may include topical therapies for symptomatic relief. In cases of any severe or persistent adverse reactions, temporary treatment interruption, dose modification, or permanent discontinuation of NEXAVAR should be considered. NEXAVAR should be discontinued if Stevens-Johnson syndrome or toxic epidermal necrolysis are suspected as these may be life threatening
- Gastrointestinal perforation was an uncommon adverse reaction and has been reported in less than 1% of patients taking NEXAVAR. Discontinue NEXAVAR in the event of a gastrointestinal perforation
- Patients taking concomitant warfarin should be monitored regularly for changes in prothrombin time (PT), International Normalized Ratio (INR), or clinical bleeding episodes
- Temporary interruption of NEXAVAR therapy is recommended in patients undergoing major surgical procedures
- NEXAVAR, in combination with gemcitabine/cisplatin, is not recommended in patients with squamous cell lung cancer. The safety and effectiveness of NEXAVAR has not been established in patients with non-small cell lung cancer

- NEXAVAR can prolong the QT/QTc interval and increase the risk for ventricular arrhythmias. Avoid use in patients with congenital long QT syndrome and monitor patients with congestive heart failure, bradyarrhythmias, drugs known to prolong the QT interval, and electrolyte abnormalities. Interrupt NEXAVAR if QTc interval is greater than 500 milliseconds or for an increase from baseline of 60 milliseconds or greater
- Drug-induced hepatitis with NEXAVAR may result in hepatic failure and death. Liver function tests should be monitored regularly and in cases of increased transaminases without alternative explanation NEXAVAR should be discontinued
- NEXAVAR may cause fetal harm when administered to a pregnant woman. Women of child-bearing potential should be advised to avoid becoming pregnant while on NEXAVAR and female patients should also be advised against breastfeeding while receiving NEXAVAR
- In DTC, NEXAVAR impairs exogenous thyroid suppression. Elevation of thyroid stimulating hormone (TSH) level above 0.5 mU/L was observed in 41% of NEXAVAR-treated patients as compared with 16% of placebo-treated patients in the DTC study. Monitor TSH levels monthly and adjust thyroid replacement medication as needed in patients with DTC
- Elevations in serum lipase and reductions in serum phosphate of unknown etiology have been associated with NEXAVAR
- Avoid concomitant use of strong CYP3A4 inducers, when possible, because inducers can decrease the systemic exposure of sorafenib. NEXAVAR exposure decreases when co-administered with oral neomycin. Effects of other antibiotics on NEXAVAR pharmacokinetics have not been studied
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You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1.800.FDA.1088. For important risk and use information about NEXAVAR, please see the full Prescribing Information at www.nexavar-us.com.

Work with your multidisciplinary team and referring physicians to identify potential candidates for NEXAVAR therapy.

*DECISION=Stu**D**y of soraf**E**nib in lo**C**ally advanced or metastat**I**c patient**S** with radioactive Iodine refractory thyr**O**id ca**N**cer.[2]

†RECIST=Response Evaluation Criteria In Solid Tumors.

‡RECIST was modified by inclusion of clinical progression of bone lesions based on the need for external beam radiation (4.4% of progression events).

References: 1. NEXAVAR® (sorafenib) [prescribing information]. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc.; November 2013. **2.** Brose MS, Nutting CM, Sherman SI, et al. Rationale and design of DECISION: a double-blind, randomized, placebo-controlled phase III trial evaluating the efficacy and safety of sorafenib in patients with locally advanced or metastatic radioactive iodine (RAI)-refractory, differentiated thyroid cancer. *BMC Cancer*. 2011;11:349. doi:10.1186/1471-2407-11-349.

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